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Serum levels of IL-32 in patients with type 2 diabetes mellitus and its relationship with TNF-α and IL-6

Reza Fadaei[a], Nader Bagheri[b], Esfandiar Heidarian[b], Ali Nouri[b], Zahra Hesari[c], Nariman Moradi[d,e], Alireza Ahmadi[f], Reza Ahmadi[b,*]

[a] Sleep Disorders Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran
[b] Clinical Biochemistry Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran
[c] Department of Laboratory Science, Faculty of Paramedicine, Golestan University of Medical Sciences, Gorgan, Iran
[d] Department of Clinical Biochemistry, Faculty of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran
[e] Department of Clinical Biochemistry, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran
[f] Laboratory Sciences Research Center, Golestan University of Medical Sciences, Gorgan, Iran

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is an important public health worldwide. The main underlying mechanism of T2DM is insulin resistance which is associated with chronic inflammation. Interleukin-32 (IL-32) is a pro-inflammatory cytokine which has been implicated in pro-inflammatory responses of several human diseases. Previous studies have reported higher levels of IL-32 in inflammatory disease and obesity. The present study aimed to evaluate the serum concentrations of IL-32 in patients with T2DM and its association with cardiometabolic parameters.

This study was undertaken on 93 patients with TDM and 74 healthy controls. T2DM was diagnosed based on ADA criteria. Serum levels of IL-32, adiponectin, TNF-α, and IL-6 were measured by ELISA technique.

Our findings revealed independent elevated levels of IL-32 in T2DM group (1061 (841.9–1601) pg/mL) compared to the control (630.4 (331.1–830.9) pg/mL). Furthermore, it was associated with increased risk of T2DM incidence. IL-32 indicated a positive correlation with body mass index, fasting blood glucose, TNF-α, and IL-6 in patients with T2DM. Furthermore, linear regression showed independent association between IL-32 and IL-6 plus TNF-α in patients' group.

The results of the present study revealed higher levels of IL-32 in T2DM patients which have been associated with inflammatory markers. These results suggest the possible role of IL-32 in chronic inflammation in patients with T2DM.

1. Introduction

The prevalence of T2DM is rapidly increasing worldwide, which has become a major public health problem [1]. Over-nutrition, inactivity, and obesity are important risk factors for T2DM development [2]. This disease has grave consequences such as atherosclerosis, neuropathy, nephropathy, and retinopathy which lead to high morbidity and mortality [3].

Lipotoxicity, oxidative stress, ER stress, and inflammation play an important role in the development of insulin resistance [4]. Cross-sectional and prospective studies have reported perturbation of inflammatory markers in the context of T2DM [5]. For instance, several lines of evidence have indicated the role of cytokines including tumor necrosis factor alpha (TNF-α), interleukin (IL)-1b, IL-6, IL-18, and interferon-gamma in the pathogenesis of atherosclerosis [5–7].

IL-32, also called natural killer cell transcript-4 and TNF-α-induced factor, is a novel pro-inflammatory cytokine which has important functions in immune regulation [8]. It can provoke inflammation by evoking other cytokines including TNF-α, IL-1b, IL-6, and IL-8 [8,9]. It has been demonstrated that IL-32 is expressed in human peripheral blood mononuclear cells and its expression is regulated by inflammatory cytokines [10]. Therefore, it has been speculated that IL-32 is involved in inflammatory diseases [10,11]. Previous studies have reported the important role of IL-32 in human inflammatory diseases such as Crohn's disease, ulcerative colitis, and rheumatoid arthritis [12,13]. It has been found that IL-32 overexpression in high fat diet mice protects them from hepatic inflammation and steatosis [14]. However, it has been reported that IL-32 overexpression in

* Corresponding author.
E-mail address: ahmadi.r@skums.ac.ir (R. Ahmadi).

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Table 1
Anthropometric and biochemical characteristics of studied population.

Variables	Control	T2DM	p
Age (year)	56.99 ± 8.83	58.66 ± 8.42	0.215
BMI (kg/m^2)	25.65 ± 3.42	26.41 ± 4.15	0.197
Sex [male (%)]	53 (71.6)	61 (65.6)	0.406
SBP (mmHg)	128.26 ± 16.53	136.60 ± 19.36	0.003
DBP (mmHg)	79 (72.25–86.75)	80 (76–92)	0.007
FBG (mg/dL)	92.35 ± 11.45	164.47 ± 24.37	< 0.001
Insulin (μU/mL)	3.2 (2.05–5.72)	11.6 (9.25–14.6)	< 0.001
HOMA-IR	0.73 (0.43–1.24)	4.66 (3.38–6.41)	< 0.001
TG (mg/dL)	120.11 ± 44.80	162.44 ± 55.85	< 0.001
TC (mg/dL)	169.57 ± 37.61	191.99 ± 45.98	0.001
LDL-C (mg/dL)	102.53 ± 30.32	119.22 ± 37.01	0.002
HDL-C (mg/dL)	47.19 ± 6.94	42.80 ± 5.38	< 0.001
Creatinine (mg/dL)	1.13 ± 0.18	1.17 ± 0.15	0.070
AST (U/L)	17.83 ± 5.35	19.52 ± 5.84	0.056
ALT (U/L)	17.96 ± 7.55	20.17 ± 7.83	0.067
Adiponectin (μg/mL)	11.90 ± 3.67	9.53 ± 2.56	< 0.001
TNF-α (pg/mL)	21.23 (12.78–26.44)	27.58 (24.05–33.99)	< 0.001
IL-6 (pg/mL)	5.23 (4.04–6.21)	9.27 (7.2–12.53)	< 0.001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment of insulin resistance; TG, triglyceride; TC, total cholesterol; LDL-C, Low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; AST, aspartate amino transferase; ALT, alanine amino transferase; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6.

streptozotocin (STZ)-induced diabetic mice involved in pancreatic inflammation and β-cell injuries [15]. Catalan et al. showed that IL-32 knockdown in human adipocyte decreased the expression of inflammatory genes [16]. Furthermore, they reported higher adipose tissue mRNA expression and circulating levels of IL-32 in obese patients and obese T2DM patients compared to lean normal group [16].

Table 2
Odd ratio for T2DM present according to 10 units change in IL-32 serum levels.

Model	Odd ratio (95% confidence interval)	p
Crude model	1.049 (1.032–1.066)	< 0.001
Adjusted model*	1.050 (1.032–1.069)	< 0.001

* Adjusted for age, sex, BMI and medication

Accordingly, the purpose of this study was to evaluate the serum levels of IL-32 in T2DM and controls which were matched in terms of BMI and age. Also, the relationship between IL-32 and anthropometrics as well as biochemical and inflammatory cytokines was tested in the groups.

2. Study population and methods

2.1. Participants

This case control study enrolled 93 patients with T2DM and 74 healthy individuals between the ages of 55 and 75 years who presented for routine check-up in Hajar Hospital between Jun 2017 and December 2018. T2DM was diagnosed based on ADA criteria [17]. Individuals with a history of any inflammatory diseases including rheumatoid arthritis, severe kidney and liver diseases, cancer, infectious disease, stroke, and heart attack were excluded from the study. All participants provided written informed consent to participate in this study, and the

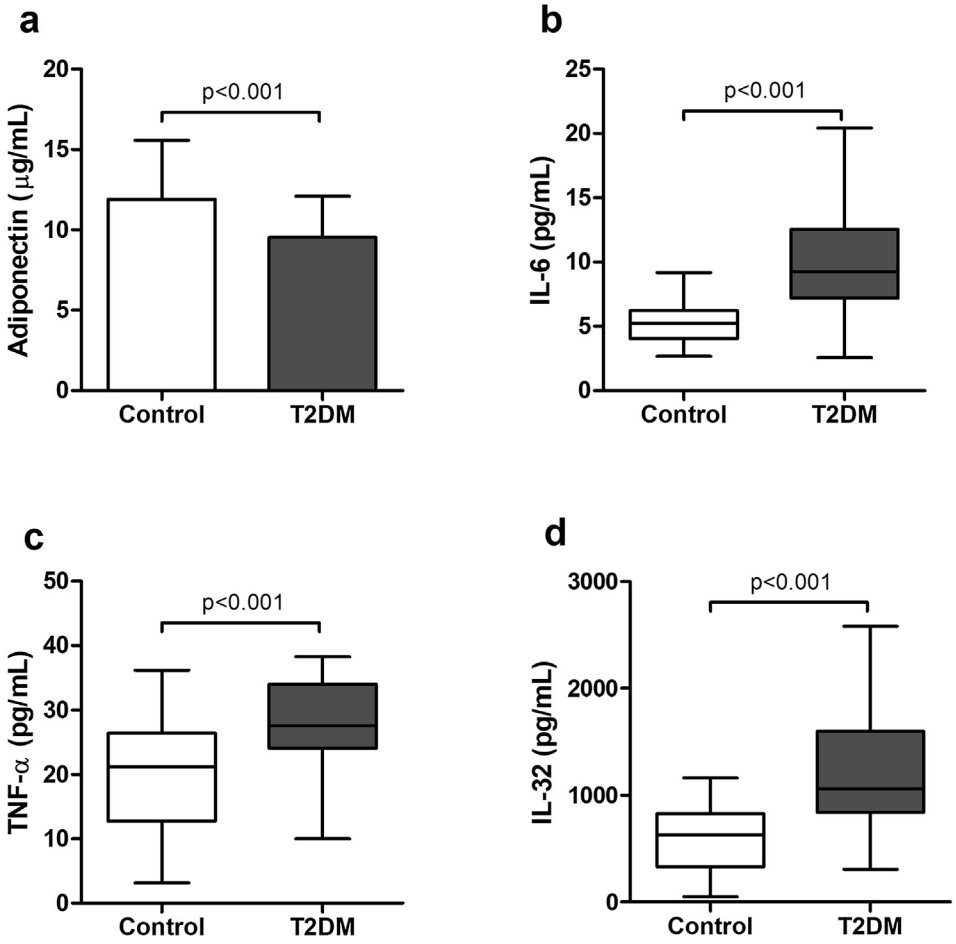

Fig. 1. Serum levels of (a) adiponectin, (b) IL-6, (c) TNF-α and (d) IL-32 in the studied groups.

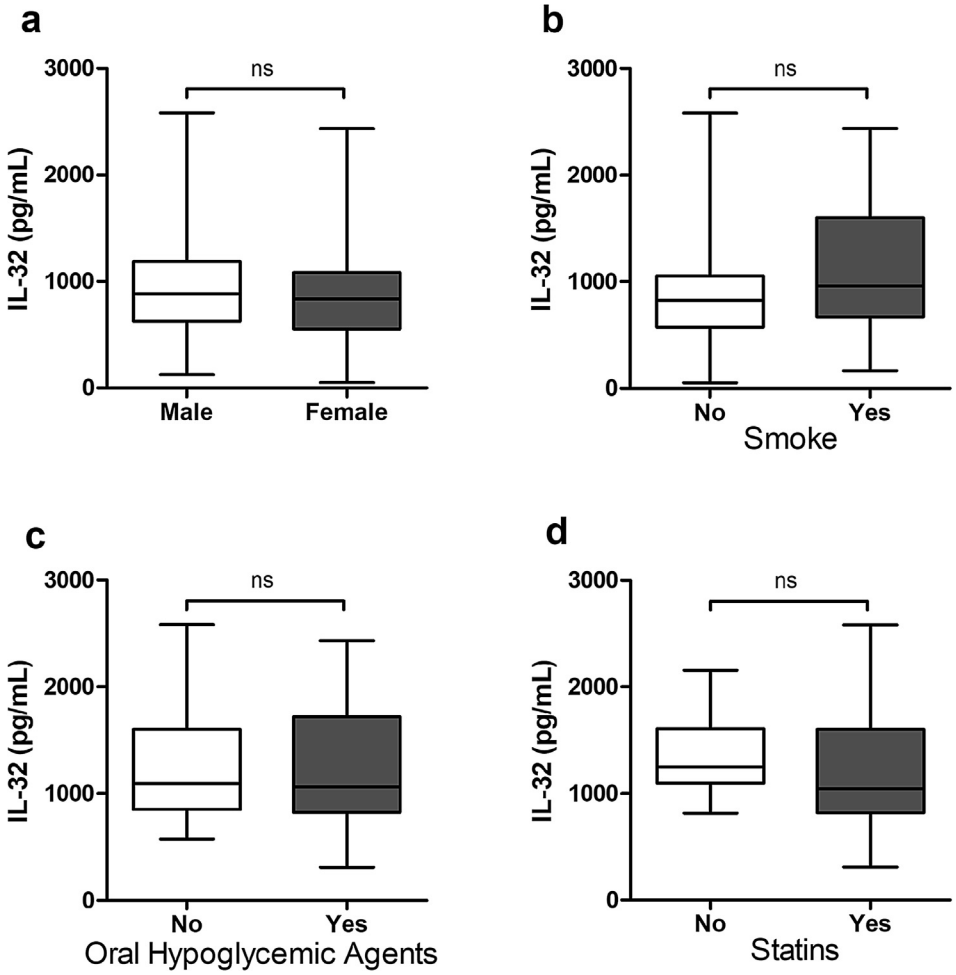

Fig. 2. (a) Serum levels of IL-32 in male group compared with female group. (b) Serum levels of IL-32 in smokers compared to non-smokers. (c) IL-32 serum levels in T2DM patients according to receiving OHA. (d) Serum levels of IL-32 in T2DM patients according to receiving statins.

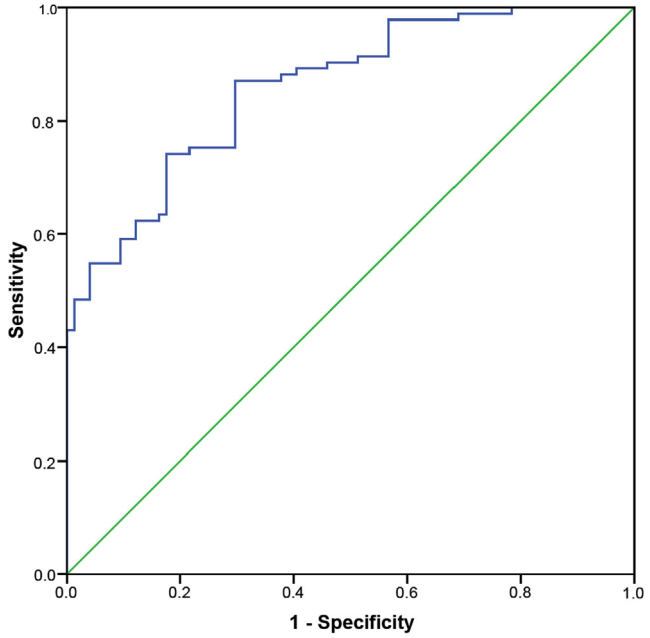

Fig. 3. ROC curve for differentiation between T2DM patients and controls according to serum levels of IL-32 (Area under curve (95% confidence interval) = 0.859 (0.805–0.913), $p < 0.001$).

study was confirmed by the Ethic Committee of Sahrekord University of Medical Sciences.

2.2. Anthropometric and laboratory evaluation

All the subjects underwent comprehensive physical examinations as well as biochemical analyses of blood. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Resting blood pressure was measured according to the standardized protocol. Blood samples were collected after a 12-h overnight fasting. Serum samples were stored at −80 °C until subsequent analyses. Fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG) and high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), alanine amino transferase (ALT), aspartate amino transferase (AST), and creatinine (Cr) were determined by enzymatic methods using Hitachi autoanalyzer. Fasting insulin was measured by ELISA kit (Monobind; USA) and the standard formula ([fasting blood glucose (mg/dl)] × [fasting blood insulin (μU/mL)/405]) was applied to calculate the homeostasis model assessment of insulin resistance (HOMA-IR).

2.3. Measurement of serum adiponectin and cytokines

Serum level of IL-32 was determined using an ELISA kit (R&D Systems; USA) with intra-assay Coefficients of Variability (CV) < 10% and Inter-assay CV < 8%. Also, the serum level of adiponectin was measured using an ELISA kit (Adipogen; South Korea) with intra- and inter-assay CV of 4.6% and 4.4%, respectively. IL-6 and TNF-α were

Table 3
Correlation and association of log IL-32 with continuous variables.

Variables	Control		T2DM	
	Pearson r	B (95% CI)	Pearson r	B (95% CI)
Age	−0.221		−0.089	
BMI	0.159		0.254*	0.008 (0.000–0.016)
SBP	−0.266*	−0.004 (−0.008–0.000)*	0.103	
Log DBP	−0.108		0.105	
FBG	0.181		0.204*	0.001 (0.000–0.003)
Log Insulin	0.063		0.096	
Log HOMA-IR	0.092		0.152	
TG	−0.075		−0.060	
TC	−0.052		0.052	
LDL-C	−0.053		0.057	
HDL-C	0.087		−0.104	
Adiponectin	0.111		−0.125	
Creatinine	0.278*	0.387 (0.042–0.733)*	−0.026	
AST	0.009		−0.182	
ALT	0.076		0.009	
Log TNF	0.101		0.409**	0.403 (0.144–0.661)**
Log IL-6	0.159		0.405**	0.278 (0.089–466)**

*p < 0.05.
*p < 0.01.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment of insulin resistance; TG, triglyceride; TC, total cholesterol; LDL-C, Low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; AST, aspartate amino transferase; ALT, alanine amino transferase; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6.

Table 4
Spearman correlation of TNF-α and IL-6 with continuous variables.

Variables	Control		T2DM	
	Log TNF	Log IL-6	Log TNF	Log IL-6
Log IL-6	0.104	1	0.342**	1
Age	0.056	−0.192	−0.008	0.013
BMI	−0.129	0.136	0.018	0.174
SBP	−0.177	−0.372**	0.015	0.129
Log DBP	−0.105	−0.168	0.053	0.047
FBG	−0.089	0.167	0.096	−0.045
Log Insulin	−0.106	0.237*	0.086	0.108
Log HOMA-IR	−0.112	0.246*	0.115	0.083
TG	−0.019	0.002	0.086	0.077
TC	0.071	0.020	0.100	−0.039
LDL-C	0.039	0.040	0.050	−0.069
HDL-C	0.134	−0.056	−0.010	−0.181
Adiponectin	−0.025	−0.007	−0.179	−0.237*
Creatinine	0.159	0.094	0.059	−0.192
AST	−0.037	−0.029	−0.144	−0.049
ALT	0.020	−0.065	−0.023	0.079

*p < 0.05.
*p < 0.01.
TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment of insulin resistance; TG, triglyceride; TC, total cholesterol; LDL-C, Low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; AST, aspartate amino transferase; ALT, alanine amino transferase.

measured using ELISA kits (R&D Systems; USA). Minimum detectable doses of IL-6 and TNF-α were 0.7 and 1.6 pg/mL, respectively.

2.4. Statistical analyses

Statistical analyses were performed using SPSS Statistics 17 for Windows (SPSS Inc., Chicago, IL, USA). Categorical data were tested by Chi-square test and presented by frequency and percentage. Data were checked for normality by Kolmogorov–Smirnov test prior to all statistical analyses. Descriptive statistics for normally distributed variables are expressed as mean ± standard deviation (SD), while non-normally distributed data are shown by mean and inter quartile range (IQR). Student's *t* test and Man-Whitney test were used to determine differences in subjects' characteristics and measured outcomes. Non-normal data were logarithmically transformed for correlation analysis. Spearman' correlation coefficients were computed for the relationship between IL-32 and all variables. Multiple linear regression was performed to check the correlated parameters with IL-32. Finally, logistic regression was conducted to evaluate the risk of T2DM according to IL-32 levels.

3. Results

3.1. Anthropometric and biochemical measurements

Demographic and clinical characteristics of the study participants are presented in Table 1. Mean age, sex, and BMI of the participants were not significantly different. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were higher in T2DM patients compared to controls. All parameters of glucose metabolism including FBG, insulin, and HOMA-IR were elevated in T2DM patients compared to controls. In addition, TG, TC, and LDL-C showed a higher concentration in T2DM patients compared to controls, while HDL-C was lower in the patient group. Markers of kidney and liver function including Cr, ALT, and AST showed no significant difference between the groups. Meanwhile, the number of smokers was higher in T2DM groups compared to controls. Finally, 13 patients used OHAs and 10 patients were under statins therapy.

3.2. Adiponectin and cytokines levels

Our findings showed that adiponectin level was significantly lower T2DM group than in the control group (Fig. 1a). However, IL-6 and TNF-α were elevated in patients compared to controls (Fig. 1b and c).

IL-32 serum levels indicated higher levels in patients with T2DM (1061 (841.9–1601) pg/mL) compared with controls (630.4 (331.1–830.9) pg/mL), (mean and SD in T2DM vs. controls respectively, (1248 ± 551.4 vs 598.4 ± 290.1 pg/mL) (Fig. 1d). In addition, the effects of possible covariates (age, sex, BMI and medications) were adjusted on IL-32 serum levels, where the difference between T2DM and control groups remained significant ($p < 0.001$). Furthermore, logistic regression indicated an independent association between IL-32 and incidence of T2DM. Note that the effects of covariates were adjusted on the model and the results remained significant (Table 2).

The potential of IL-32 for diagnosis of T2DM was tested using ROC curve analysis. The result indicated a relatively good ability for differentiation between disease status and controls using IL-32 (Area under curve (95% confidence interval) = 0.859 (0.805–0.913), $p < 0.001$) (Fig. 3).

3.3. Relation of IL-32, TNF-α and IL-6 with anthropometric as well as biochemical measurements

IL-32 showed no significant difference between male and female (Fig. 2a), and smoker and non-smoker (Fig. 2b). Meanwhile, statins and OHA therapies had no effect on IL-32 serum levels in patients with

T2DM (Fig. 2c and d). Correlation analysis revealed that IL-32 inversely correlated with SBP and positively correlated with Cr in control group, and multiple linear regression indicated independent association of IL-32 with SBP and Cr in control group (Table 3). Furthermore, IL-32 positively correlated with BMI, FBG, TNF-α, and IL-6 in T2DM group. Finally, linear regression demonstrated an independent association between IL-32 and TNF-α as well as IL-6 (Table 3).

TNF-α showed no significant correlation with continuous variables in controls, while IL-6 indicated inverse correlation with SBP and positive correlation with insulin and HOMA-IR. In addition, IL-6 demonstrated positive correlation with TNF-α and inverse correlation with adiponectin in T2DM group (Table 4).

4. Discussion

The relationship between inflammation and diabetes mellitus and insulin resistance is a matter of ongoing research [18]. It has been suggested that malfunctioning occurs through inflammation in insulin resistance and β-cell function [18]. It has been shown that levels of inflammatory markers such as IL-6, TNF-α, IL-1β, and CRP rise in patients with T2DM and targeting inflammation has been suggested as a possible therapeutic option for T2DM and its complication such as atherosclerosis, neuropathy, nephropathy, and retinopathy [19,20].

IL-32 is a cytokine involved in inflammation regulation [20–22]. It has been found that inflammation induced by ionizing radiation increased the expression of IL-32 in vascular cells [23]. Indeed, IL-32 can amplify the inflammation upon ionizing radiation [23]. Another study reported up-regulation of IL-32 in arterial specimens of atherosclerotic patients [11]. Previous studies on patients with inflammatory disease such as rheumatoid arthritis, Bechet's diseases, and IBD demonstrated higher levels of IL-32 in these patients [10,24,25]. Furthermore, a study by Catalan et Al. reported higher levels of IL-32 in obese and T2DM obese patients compared to controls [16]. In line with these results, in the present study IL-32 indicated a higher concentration in T2DM patients compared to controls, with higher IL-32 concentration being associated with risk of T2DM incidence. Furthermore, our results showed that the association between IL-32 serum levels and T2DM was independent of covariates. In Catalan et al.'s study [16], the patients were obese while the controls were lean. In the present study, groups were matched in terms of BMI and we showed that increased IL-32 in T2DM patients was independent of BMI. However, IL-32 was positively correlated with BMI in T2DM patients. Catalan et al. reported elevated IL-32 expression in adipose tissue of obese subjects and they found a positive association between IL-32 and BMI [16].

A study found that IL-32 overexpression exacerbates β-cell injuries and inflammation of pancreas in STZ-induced T1DM mice [15]. In the present study, IL-32 showed a weak positive correlation with FBG and no correlation with insulin or HOMA-IR in the patient group. In addition, serum levels of IL-32 showed no significant difference between 13 T2DM patients who received OHA compared with newly diagnosed patients. Based on these results, IL-32 seems to have a weak association with glucose metabolism. Note that this study has had a cross-sectional design and could not conclude a causal relationship; therefore more studies are needed to evaluate the effects of IL-32 on glucose and insulin metabolism. IL-32 exhibited a positive correlation with SBP and Cr in controls. Previous studies have reported increased levels of IL-32 in response to hypoxia [26], though its relationship with blood pressure and kidney function is not clear and more studies are warranted in this regard.

It has been reported that IL-32 affects the inflammatory reactions and promotes production of inflammatory cytokines such as TNF-α, IL-6, IL-1β, and IL-8 [8,27]. In addition, IL-32 accelerates monocyte to macrophage differentiation [28]. Further, LPS and TNF-α elevate IL-32 expression while IL-13 decreases its expression [27]. In this regard, IL-32 levels in synovial biopsies of patients with rheumatoid arthritis revealed a positive association with severity of inflammation [29]. In the present study, IL-32 was found to be correlated with inflammatory cytokines (IL-6 and TNF-α); however, IL-32 demonstrated no correlation with inflammatory cytokines in controls. These results suggested a pro-inflammatory role for IL-32 in T2DM where increased inflammation in T2DM could be partially related to increased IL-32 levels.

Six different isoforms of IL-32 have been identified (α, β, γ, δ, ε and ζ) [30] and the ELISA kit in the present study measured three isoforms, α, β and γ. IL-32α and IL-32β are suggested to be the major expressed isoforms and IL-32γ introduced as the most active form [31]. A limitation of the present study was that each isoform was not measured specifically, and further studies needed to establish the role of each isoform in the pathogenesis of insulin resistance and T2DM.

In conclusion, IL-32 increased in T2DM patients and it showed a positive association with inflammatory cytokines in these patients. These results suggested involvement of IL-32 in chronic inflammation in the context of T2DM. Nevertheless, further studies are required to evaluate the possible causal relationship between IL-32 and pathogenesis of T2DM.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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